(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 091 761**
B1

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **19.11.87**

(51) Int. Cl.⁴: **C 07 D 277/34** // C07D277/54

(21) Application number: **83301847.6**

(22) Date of filing: **31.03.83**

(54) **Thiazolidine derivatives and production thereof.**

(30) Priority: **13.04.82 JP 62223/82**

(43) Date of publication of application:
19.10.83 Bulletin 83/42

(45) Publication of the grant of the patent:
19.11.87 Bulletin 87/47

(84) Designated Contracting States:
BE CH DE FR GB IT LI NL SE

(56) References cited:
EP-A-0 033 617
FR-A-1 222 411
FR-A-2 100 632

(73) Proprietor: **Takeda Chemical Industries, Ltd.**
27, Doshomachi 2-chome Higashi-ku
Osaka-shi Osaka, 541 (JP)
(73) Proprietor: **Senju Seiyaku Kabushiki Kaisha also known as Senju Pharmaceutical Co. Ltd.**
6-1, Hiranomachi 3-chome
Higashi-ku Osaka (JP)

(72) Inventor: **Kawamatsu, Yutaka**
15-3, Oharano-kamisatotorimicho
Nishikyo-ku Kyoto 610-11 (JP)
Inventor: **Fujita, Takeshi**
13-15, Nagaodai 1-chome
Takarazuka Hyogo 665 (JP)
Inventor: **Yamamoto, Yujiro**
C5-305, 1 Momoyamadai 1-chome
Suita Osaka 565 (JP)

(74) Representative: **Laredo, Jack Joseph et al**
Elkington and Fife High Holborn House
52/54 High Holborn
London, WC1V 6SH (GB)

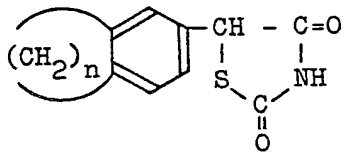
Courier Press, Leamington Spa, England.

EP 0 091 761 B1

Description

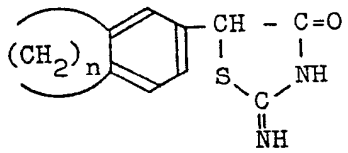
This invention relates to novel thiazolidine derivatives useful as prophylactic and therapeutic agents of diabetic complications such as diabetic cataract or diabetic neuropathy, and the production thereof.

More specifically, this invention relates to thiazolidine derivatives representable by the formula;



(I)

wherein *n* denotes an integer of 3 to 6 and preferably 3, 4 and 5, and a method for production of the compound (I) which comprises hydrolyzing a compound representable by the formula:



(II)

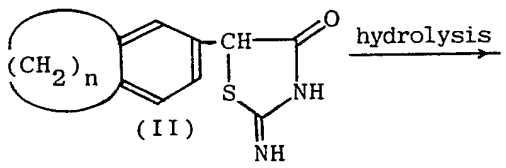
wherein *n* has the same meaning as above.

The compounds representable by the general formula (I) are acid substances capable of forming alkali metal or alkaline earth metal salts e.g. sodium salts, potassium salts or calcium salts.

Thiazolidine derivatives (I) or the alkali metal or alkaline earth metal salts thereof of this invention are strong aldose reductase inhibitors and remarkably inhibit the accumulation of sorbitol in lens or nerve fiber in diabetic rats induced by streptozotosin, and they are used for prophylaxis or therapy of diabetic cataract or diabetic neuropathy, for example, in mammals, for instance, mouse, rat, dog and human being.

Further, the compounds (I) or their alkali metal or alkaline earth metal salts are less toxic, the oral LD_{50} for, for example, 5-(5,6,7,8-tetrahydro-2-naphthyl)thioazolidine-2,4-dione in mice being not less than 1000 mg., and they can be safely administered for a long period of time. When the compounds (I) or their alkali metal or alkaline earth metal salts are administered for ophthalmic use, they do not cause irritation and can inhibit accumulation of sorbitol in the lens, and thus can be of ophthalmic use in treating cataract. The compounds (I) or their alkali metal or alkaline earth metal salts may, for example, be administered orally in such dosage forms as tablets, capsules, powders and granules, parenterally in the form of injections and pellets, or locally as ophthalmic solutions. The dosage is usually 50 mg. to 1000 mg. daily per adult human, when given orally, in 1 to 4 divided doses a day. For ophthalmic use, 0.001 to 1% ophthalmic solution is desirably administered to the eye at the frequency of 3 to 5 times daily, one to a few drops at a time.

The thiazolidine derivatives (I) of this invention can be produced in the folowing manner:



(II) (I)

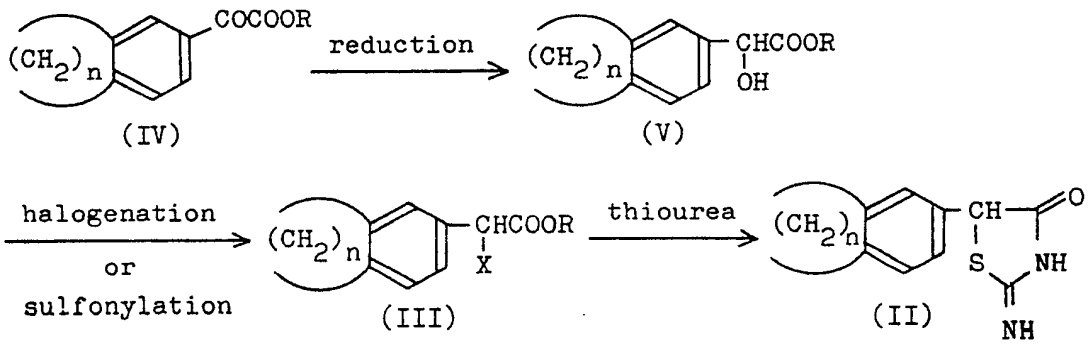
In the formulae, *n* has the same meaning as above.

The hydrolysis is conducted in the presence of a mineral acid in a suitable solvent.

As the suitable solvents, there may for example, be mentioned alkanols, e.g. methanol, ethanol, propanol or methoxyethanol, ethers, e.g. tetrahydrofuran or dioxane, acetone, dimethylformamide, dimethyl sulfoxide or sulforane. The mineral acid may be, for example, sulfuric acid or hydrochloric acid. The amount of the acid to be added is usually within the range of from 1 mole to 50 moles, preferably from 2 to 30 moles relative to the compound (II) employed. The amount of water to be added is usually in large axcess. The hydrolysis reaction is conducted at a temperature within the range of from 30 to 150°C.

The resulting compound (I) can be isolated and purified by conventional means such as concentration, solvent-extraction, recrystallization or chromatography. The compound (I) which is an acid compound can be converted to a salt with an alkali metal or alkaline earth metal such as sodium, potassium or calcium.

The compound (II) can be synthesized, for example, in the following manner:



In the formulae, R represents hydrogen or an alkyl or aralkyl group, X represents a group to be eliminated, and *n* has the same meaning as above.

As the alkyl group represented by R, the preferred groups are those having 1—4 carbon atoms, e.g. methyl, ethyl, propyl, isopropyl, *n*-butyl, isobutyl, sec.-butyl or *t*-butyl. As the aralkyl group represented by R, there may preferably be mentioned a phenyl lower alkyl, e.g. benzyl or phenylethyl.

As the group to be eliminated representable by X are exemplified halogen, e.g. chlorine or bromine, or a sulfonyloxy group, e.g. mesyloxy, tosyloxy or benzenesulfonyloxy. *n* denotes an integer of 3—6, and especially preferred are 3, 4 and 5.

Glyoxylic acid derivatives representable by the formula (IV) and their reduction products (V) can be synthesized by the method described in Austrian Patent No. 344153 (1978) (C. A. *89,* P179741e (1978)) or a method analogous thereto.

The compound (III) can be obtained by halogenation or sulfonylation of the compound (V).

The halogenation is carried out by reacting a halogenating agent such as phosphorus tribromide, thionyl chloride and phosphorus oxychloride with the compound (V) in the absence or presence of a suitable solvent such as dichloromethane and chloroform. The reaction is preferably conducted at an elevated temperature, for example, 20 to 100°C.

Sulfonylation of a compound (V) can be conducted by reacting the compound (V) with a sulfonylating agent e.g. mesyl chloride, tosyl chloride or benzenesulfonyl chloride, at 0—60°C in a suitable solvent, e.g. benzene, ethyl acetate, dichloromethane or chloroform, in the presence of a base, e.g. pyridine or triethylamine.

The compound (III) thus produced is allowed to react with thiourea to synthesize a compound (II), which is then subjected to hydrolysis to yield the desired compound (I). The reaction between a compound (III) and thiourea is usually conducted in a solvent.

The solvents are exemplified by alkanols, e.g. methanol, ethanol, propanol or methoxyethanol, ethers, e.g. tetrahydrofuran or dioxane, acetone, dimethylformamide, dimethylsulfoxide or sulfolane. The amount of thiourea to be used is preferably 1—2 mol. relative to 1 mol. of the compound (III) employed. The reaction temperature usually ranges from 50°C to 150°C, preferably 60 to 130°C.

The thus-produced compound (II) can be isolated in an optional purity by means of a conventional separation and purification method, for example, concentration, solvent-extraction, recrystallization or chromatography, or can be converted to the compound (I) by subjecting the reaction mixture to the subsequent hydrolysis directly without isolating the compound (II).

The following reference examples, working examples and experimental data are given to further illustrate this invention.

Reference Example 1

Anhydrous aluminum chloride (9.1 g) was suspended in dichloromethane (80 ml). To the suspension was added dropwise, while stirring under cooling, ethoxalyl chloride (9.2 g), followed by adding thereto 6,7,8,9-tetrahydro-5H-benzocycloheptadiene (9.0 g) dissolved in dichloromethane (10 ml). The mixture was stirred for 30 minutes under ice-cooling, and poured into ice-water. The resulting organic layer was separated, washed with water and dried over anhydrous magnesium sulfate, and then the solvent was evaporated off. The residue was subjected to distillation under reduced pressure to leave 10.7 g (70.4%) of ethyl 6,7,8,9-tetrahydro-5H-benzocycloheptadien-2-yl-glyoxylate as an oily substance, b.p. 153—155°C/0.2 mmHg.

IR (Neat): 1735, 1685 cm^{-1}.

NMR ($CDCl_3$) δ: 1.39 (3H, t, J=7), 1.75 (6H, broad s), 2.65—2.95 (4H, m), 4.40 (2H, q, J=7), 7.10 (1H, d, J=9), 7.6(2H, m).

Reference Example 2

By the same procedure as that in Reference Example 1, except for employing Tetralin® as the starting material, ethyl 5,6,7,8-tetrahydro-2-naphthylglyoxylate, b.p. 148—153°/0.3 mmHg. was prepared. The yield was 70.5%.

IR (Neat): 1735, 1680 cm^{-1}.

NMR ($CDCl_3$) δ: 1.38(2H, t, J=7), 1.6—2.0 (4H, m), 2.75 (4H, broad s), 4.40 (2H, q, J=7), 7.10 (1H, d, J=9), 7.6 (2H, m).

Reference Example 3

By the same procedure as that in Reference Example 1, except for employing indane as the starting material, ethyl 5-indanylglyoxylate was prepared. The yield was 74.8%.

IR (Neat): 1735, 1680 cm^{-1}.

NMR ($CDCl^3$) δ: 1.40 (3H, t, J=7), 1.8—2.4 (2H, m), 2.93 (4H, t, J=7), 4.40 (2H, q, J=7), 7.18 (1H, d, J=9), 7.5—7.7 (2H, m).

Reference Example 4

To ethyl 6,7,8,9-tetrahydro-5H-cycloheptadien-2-yl glyoxylate (10.3 g) dissolved in ethanol (50 ml) was added sodium borohydride (0.95 g) under ice-cooling, and the mixture was then stirred for 30 minutes. To the mixture was added dropwise acetic acid (4 ml), and the whole mixture was poured into water, followed by extraction with ethyl ether. The ether layer was washed with water and a saturated aqueous solution of sodium bicarbonate and water, in that order, then dried over anhydrous magnesium sulfate. Removal of ethylether by evaporation left ethyl 2 - hydroxy - 2 - (6,7,8,9 - tetrahydro - 5H - benzocycloheptadien - 2 - yl)acetate as an oily product. The yield was 10.48 (100%).

IR (Neat): 3470, 1730 cm^{-1}.

NMR ($CDCl_3$): δ 1.20 (3H, t, J=7), 1.7 (6H, broad s), 2.6—2.9 (4H, m), 3.57 (1H, d, J=6, D_2O disappear), 4.18 (2H, q, J=7), 5.00 (1H, d, J=6, D_2O changed to s), 7.00 (3H, broad s).

Reference Example 5

Ethyl 5,6,7,8-tetrahydro-2-naphthylglyoxylate was subjected to reduction in the same manner as in Reference Example 4 to prepare ethyl 2 - hydroxy - 2 - (5,6,7,8 - tetrahydro - 2 - naphthyl)acetate as an oily product. The yield was 92.8%.

IR (Neat): 3480, 1735 cm^{-1}.

NMR ($CDCl_3$) δ: 1.18 (3H, t, J=7), 1.6—2.0 (4H, m), 2.75 (4H, broad s), 3.60 (1H, broad s, D_2O disappear), 4.18 (2H, q, J=7), 5.03 (1H, s), 6.8—7.2 (3H, m).

Reference Example 6

Ethyl 5-indanylglyoxylate was subjected to reduction in the same manner as in Reference Example 4 to prepare ethyl 2-hydroxy-2-(5-indanyl)acetate as an oily product. The yield was 92.9%.

IR (Neat): 3480, 1735 cm^{-1}.

NMR ($CDCl_3$) δ: 1.17 (3H, t, J=7), 1.8—2.4 (2H, m), 2.83 (4H, t, J=7), 3.80 (1H, d, J=6, D_2O disappear), 4.13 (2H, q, J=7), 5.05 (1H, d, J=6, D_2O change to s), 7.1—7.4 (3H, m).

Reference Example 7

A mixture of ethyl 2 - hydroxy - 2 - (6,7,8,9 - tetrahydro - (5H - benzocycloheptadien - 2 - yl)acetate (10.0 g) and thionyl chloride (20 ml) was subjected to reflux for one hour. Excess thionyl chloride was evaporated off under reduced pressure. The remaining oily substance was further subjected to distillation under reduced pressure to leave ethyl 2 - chloro - 2 - (6,7,8,9 - tetrahydro - 5H - benzocycloheptadien - 2 - yl) acetate as an oily product, b.p. 145—148°C/0.2 mmHg. The yield was 9.5 g (88.8%).

IR (Neat): 1750 cm^{-1}.

NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7), 1.7 (6H, broad s), 2.65—2.95 (4H, m), 4.17 (2H, q, J=7), 5.22 (1H, s), 7.0—7.3 (3H; m).

Reference Example 8

Ethyl 2-hydroxy-2-(5,6,7,8-tetrahydro-2-naphthyl)acetate was processed in the same manner as in Reference Example 7 to prepare ethyl 2-chloro-2-(5,6,7,8-tetrahydro-2-naphthyl)acetate as an oily product, b.p. 139—142°C/0.3 mmHg. The yield was 94.5%.

IR (Neat): 1750 cm^{-1}.

NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7), 1.6—2.0 (4H, m), 2.75 (4H, broad s), 4.18 (2H, q, J=7), 5.25 (1H, s), 6.9—7.4 (3H, m).

Reference Example 9

Ethyl 2-hydroxy-2-(5-indanyl)acetate was processed in a manner similar to that of Reference Example 7 to give ethyl 2-chloro-2-(5-indanyl)acetate as an oily substance, b.p. 128—132°C/0.3 mmHg. The yield was 92.1%.

IR Neat): 1750 cm^{-1}.

NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7), 1.8—2.2 (2H, m), 2.83 (4H, t, J=7), 4.15 (2H, q, J=7), 5.25 (1H, s), 7.0—7.3 (3H, m).

Example 1

Thiourea (3.0 g) was added to ethyl 2 - chloro - 2 - (6,7,8,9 - tetrahydro - 5H - benzocycloheptadien - 2 - yl)acetate (9.0 g) dissolved in ethanol (100 ml). The mixture was stirred for two hours under reflux, and 2*N*—HCl (50 ml) was added thereto. The mixture was refluxed a further 12 hours, cooled and poured into water. The resulting crystals were collected by filtration to yield 8.0 g (90.9%) of 5 - (6,7,8,9 - tetrahydro - 5H - benzocycloheptadien - 2 - yl)thiazolidine - 2,4 - dione. Recrystallization from 80% aqueous ethanol yielded colorless prisms, m.p. 137—138°C.

Elemental Analysis for $C_{14}H_{15}NO_2S$

Calcd.: C 64.59; H 5.42; N 5.38

Found: C 64.33; H 5.72; N 5.15

Example 2

Ethyl 2 - chloro - 2 - (5,6,7,8 - tetrahydro - 2 - naphthyl)acetate was allowed to react with thiourea in a manner similar to that in Example 1, then the reaction mixture was subjected to hydrolysis to yield crystals of 5 - (5,6,7,8 - tetrahydro - 2 - naphthyl)thiazolidine - 2,4 - dione. The yield was 92.3%. Recrystallization from 75% aqueous ethanol gave colorless plates, m.p. 157—158°C.

Elemental Analysis for $C_{13}H_{13}NO_2S$

Calcd.: C 63.14; H 5.30; N 5.66

Found: C 63.35; H 5.15; N 5.66

Example 3

2.47 g of 5 - (5,6,7,8 - tetrahydro - 2 - naphthyl)thiazolidine - 2,4 - dione was dissolved in 100 ml of ethyl acetate. To the solution was added 2 ml of 28% methanol solution of sodium methylate, whereupon fine crystals precipitated. Ethyl acetate was evaporated off. To the residue was added ethyl ether, and the resulting fine crystals were collected by filtration. Recrystallization from methanol yielded 2.01 g (74.7%) of 5 - (5,6,7,8 - tetrahydro - 2 - naphthyl)thiazolidine - 2,4 - dione as prisms. The melting point was higher than 300°C.

IR (Nujol) cm^{-1}: 1670, 1565, 1320, 1250.

NMR (d_6-DMSO) δ: 1.70 (4H, bs), 2.32 (4H, bs), 4.97 (1H, s), 6.93 (3H, s).

Elemental Analysis for $C_{13}H_{12}NO_2S \cdot Na$

Calcd.: C 57.98; H 4.49; N 5.20

Found: C 57.91; H 4.28; N 5.49

Example 4

Ethyl 2-chloro-2-(5-indanyl)acetate was allowed to react with thiourea in a manner similar to Example 1. The reaction mixture was then subjected to hydrolysis to yield crystals of 5-(5-indanyl)thiazolidine-2,4-dione. The yield was 83.3%. Recrystallization from ethanol afforded colorless plates, m.p. 124—125°C.

Elemental Analysis for $C_{12}H_{11}NO_2S$

Calcd.: C 61.78; H 4.75; N 6.00

Found: C 61.67; H 4.67; N 5.89

Experiment

(1) Tert compounds

The following Experiments were carried out on the compounds of the two groups, one group consisting of the present compounds and the other group consisting of the known compounds which are thought to be the closest in chemical structure to the present compounds and are disclosed in European Patent Publication No. 33617.

(2) Aldose Reductase Inhibitory Action

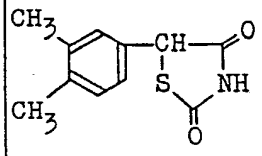
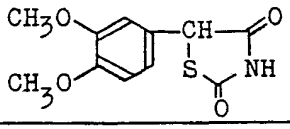
Aldose reductase inhibitory action was assayed in accordance with the method disclosed in S. Haymen et al. in Journal of Biological Chemistry, Vol. 240, p. 877 (1965) and that disclosed by Jin H. Kinoshita et al. in Metabolism, Vol. 28, Nr. 4, Suppl. 1, 462 (1979). The enzyme used in the assay was a partially purified aldose reductase preparation from human placenta. The results for the respective compounds were expressed as % inhibition at the concentration of 10^{-6} mole and are shown in Table 1.

(3) Inhibition of Sorbitol Accumulation in the tissue of rats

Sprague-Dawley rats (male, 5—7 weeks old, five rats/group) were fasted for 18 hours. The rats were made diabetic by an intravenous injection of 70 mg/kg of streptozotocin (Produced by Cal Biochem) at the site of the tail under ether anesthesia. After the administration of streptozotocin, these rats were administered orally with 25 mg/kg of the test compounds (5% suspension of gum-arabica) for two days twice a day (at 9.00 a.m. and at 4.00 p.m.). During this period, these rats were allowed to freely accede to CE—2 feedstuff (Produced by Clea Japan) and water while determining blood-sugar level of each animal. On the morning of the third day, these rats were decapitated and bled, then the lens and sciatic nerve were quickly excised. The respective contents of sorbitol in the lens and sciatic nerve were determined by the enzymatic assay method described by R. S. Clements et al., in Science, *166* p. 1007 (1969) applied to the extracts of these organs obtained by the method described by M. J. Peterson et al., in Metabolism, *28,* 456 (1979).

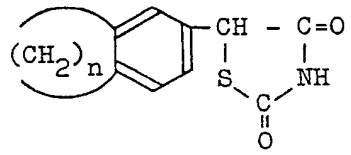
The results are shown in Table 1 below as % inhibition relative to the control. Incidentally, no significant difference in blood-sugar level was observed between the group of test animals to which the test compounds were administered and the control group of the test animals to which no test compounds were administered.

Table 1

Test Compounds				Aldose Reductase Inhibition % 10^{-6}M	Inhibition of Sorbitol Accumulation (%)	
					Lens	Sciatic Nerve
Present Compounds	Compound (I)	n	3	30.0	62	66
			4	36.0	73	79
			5	34.0	65	83
Comparative compounds				35.8	18	5
				57.1	62	-2

Claims

1. A compound of the formula:



(I)

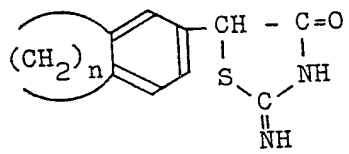
wherein *n* denotes an integer of 3 to 6, or an alkali metal or alkaline earth metal salt thereof.

2. A compound as claimed in Claim 1, wherein *n* is 3.

3. A compound as claimed in Claim 1, wherein *n* is 4.

4. A compound as claimed in Claim 1, wherein *n* is 5.

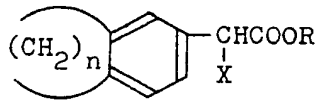
5. A method of producing a compound of the formula: (I) as defined in Claim 1 wherein *n* denotes an integer of 3 to 6, which comprises hydrolysing a compound of the formula:



(II)

wherein *n* has the same meaning as defined above, in the presence of a mineral acid and at a temperature in the range from 30 to 150°C and when necessary reacting the compound of formula (I) with an alkali metal base or with an alkaline earth metal base in order to obtain the corresponding alkali or alkaline earth metal salt.

6. A method as claimed in Claim 5, wherein the compound of the formula (II) is one prepared by reacting with thiourea a compound of the formula:



(III)

wherein R represents hydrogen, or an alkyl or aralkyl group, X represents a group to be eliminated and *n* has the same meaning as defined above.

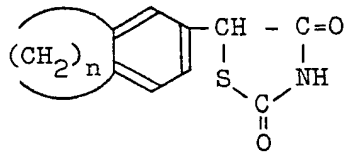
7. A method as claimed in Claim 6, wherein the reaction is carried out at a temperature ranging from 50 to 150°C in a suitable solvent.

8. A pharmaceutical composition which comprises, as an active ingredient, an effective amount of a compound as claimed in any one of Claims 1 to 4 in association with a pharmaceutically acceptable carrier or excipient therefor.

9. A compound of the formula (I) as defined in Claim 1 for use in the preparation of a medicament for diabetic prophylaxis and/or therapy.

Patentansprüche

1. Verbindung der Formel



(I)

in der

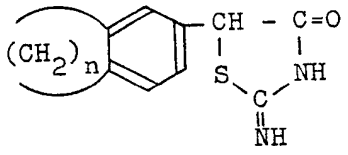
n eine ganze Zahl von 3 bis 6 bezeichnet, oder deren Alkalimetall- oder Erdalkalimetall-Salz.

2. Verbindung nach Anspruch 1, worin n 3 ist.

3. Verbindung nach Anspruch 1, worin n 4 ist.

4. Verbindung nach Anspruch 1, worin n 5 ist.

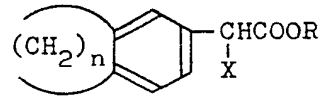
5. Verfahren zur Herstellung einer Verbindung der Formel (I) nach Anspruch 1, in der n eine ganze Zahl von 3 bis 6 bezeichnet, durch Hydrolysieren einer Verbindung der Formel



(II)

in der n die oben angegebene Bedeutung hat, in Gegenwart einer Mineralsäure und bei einer Temperatur im Bereich von 30°C bis 150°C und erforderlichenfalls Umsetzung der Verbindung der Formel (I) mit einer Alkalimetall-Base oder mit einer Erdalkalimetall-Base zur Gewinnung des entsprechenden Alkali- oder Erdalkalimetall-Salzes.

6. Verfahren nach Anspruch 5, worin die Verbindung der Formel (II) eine ist, die durch Umsetzung einer Verbindung der Formel



(III)

in der

R Wasserstoff oder eine Alkyl- oder Aralkyl-Gruppe bezeichnet,

X eine zu eliminierende Gruppe bezeichnet und

n die oben angegebene Bedeutung hat, mit Thioharnstoff hergestellt ist.

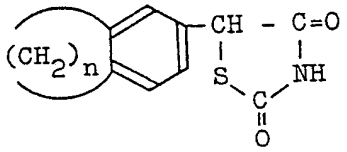
7. Verfahren nach Anspruch 6, wobei die Reaktion bei einer Temperatur im Bereich von 50°C bis 150°C in einem geeigneten Lösungsmittel durchgeführt wird.

8. Pharmazeutische Zusammensetzung, umfassend als Wirkstoff eine wirksame Menge einer Verbindung nach irgendeinem der Ansprüche 1 bis 4 in Verbindung mit einem pharmazeutisch annehmbaren Träger oder Streckmittel für diese.

9. Verbindung der Formel (I) nach Anspruch 1 zur Verwendung bei der Herstellung eines Medikaments zur Diabetes-Prophylaxe und/oder -Therapie.

Revendications

1. Composé de formule:



(I)

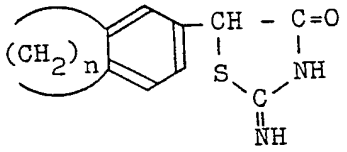
dans laquelle n représente un nombre entier de 3 à 6, ou un sel de métal alcalin ou de métal alcalino-terreux de celui-ci.

2. Composé selon la revendication 1, dans lequel n a la valeur 3.

3. Composé selon la revendication 1, dans lequel n a la valeur 4.

4. Composé selon la revendication 1, dans lequel n a la valeur 5.

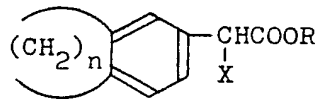
5. Procédé de préparation d'un composé de formule (I) tel que défini à la revendication 1, dans lequel n représente un nombre entier de 3 à 6, selon lequel on hydrolyse un composé de formule:



(II)

dans laquelle n a la même signification qu'indiqué ci-dessus, en présence d'acide minéral et à une température dans le domaine de 30 à 150°C et, si nécessaire, on fait réagir le composé de formule (I) avec une base d'un métal alcalin ou avec une base d'un métal alcalino-terreux, afin d'obtenir le sel de métal alcalin ou alcalino-terreux correspondant.

6. Procédé selon la revendication 5, dans lequel le composé de formule (II) est préparé en faisant réagir avec la thiourée un composé de formule:



(III)

dans laquelle R représente l'hydrogène ou un groupe alkyle ou aralkyle, X représente un groupe susceptible d'être éliminé et n a la même signification qu'indiqué ci-dessus.

7. Procédé selon la revendication 6, dans lequel la réaction est effectuée à une température située dans le domaine de 50 à 150°C, dans un solvant approprié.

8. Composition pharmaceutique qui comprend, comme substance active, une quantité efficace d'un composé selon l'une quelconque des revendications 1 à 4, en association avec une matière de support ou un excipient pharmaceutiquement acceptable.

9. Composé de formule (I) tel que défini à la revendication 1, pour son utilisation dans la préparation d'un médicament pour le traitement prophylactique et/ou curatif du diabète.